The acyclic dienamine–indoloacrylate addition route to catharanthine

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ABSTRACT

Condensation of methyl 3-benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (**3**) with methyl *Z*-4-formylhex-3-enoate (**6**) gave cis-fused dimethyl 5-benzyl-4-ethyl-2,4a,5,6,7,12-hexahydro-1*H*-benzo[2,3]azepino[4,5-*b*]indole-2,12b-dicarboxylate and its trans-fused diastereomer. Selective reduction of the less hindered ester group with sodium borohydride to an alcohol ester, tosylation, debenzylation, and cyclization gave racemic catharanthine (**1**).

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1. Introduction

Syntheses of the isoquinuclidine-containing indole alkaloids catharanthine (**1**), coronaridine (**2**), and bioactive congeners of the latter have been obtained by three different routes. The syntheses of catharanthine were based either on key intramolecular[1] or intermolecular[2] Diels–Alder additions of an acrylate to a dihydropyridine, mimicking the biogenetic postulate[3] for the natural origin of catharanthine (**1**, Scheme 1).

For syntheses of coronaridine and its congeners[4–6] intramolecular Diels–Alder addition of an indoloacrylate to an acyclic enamine moiety gave *seco*-Ψ-vincadifformine-type products that could then undergo reductive cleavage to *seco*-cleavamines, their cyclization and rearrangement to isoquinuclidine-containing structures (Scheme 2).

It became of interest to us to see if an indoloacrylate with a pendant acyclic dienamine substituent would react in either of these two alternative 2+4 (perhaps stepwise) cycloaddition modes. An intramolecular reaction of an acyclic dienamine, analogous to

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Scheme 1.

stereochemistry of the product was established by an X-ray structure,[7b] and some congeners could be made using other unsaturated aldehydes.[7] These results suggested that acyclic dienamines could react as the diene component in intramolecular 4+2 cycloadditions with indoloacrylates in analogy to Scheme 1.

2. Results and discussion

Having established the mode of intramolecular additions of an indoloacrylate as a dienophile to acyclic dienamines, as in Scheme 1, rather than as a diene, as in Scheme 2, it remained to establish this reaction for dienamines with a terminal electron withdrawing substituent. If successful, we could consider its application to a new synthesis of catharanthine (**1**) that might be extended to indoloazepines with a chiral N_b-substituent,[5,8] to provide enantioselectivity, unavailable for strategies as those depicted in Scheme 1. Five critical obstacles had to be overcome:

1. The C/D ring juncture must be cis, rather than trans as found in product **4** (Scheme 3) in order to enable a subsequent formation of the isoquinuclidine core of the iboga alkaloids.
2. Crotonals with a terminal alkyl substituent, e.g., 2-pentenal, were found to give an epimeric mixture of this substituent in the cyclohexene product, while a 1,4-cis arrangement of the amine and terminal substituents is required for cyclization to an isoquinuclidine.
3. An α-alkyl substituent on the crotonal seemed to necessitate more forcing reaction conditions such as heating in xylene with a 5-fold excess of the aldehyde. However, we had seen earlier that the indoloazepine **3** rearranges irreversibly to an α-methylenelactam on heating in xylene.[8]
4. Formation of an isoquinuclidine from a tetracyclic 1,4-cis-substituted aminocyclohexene, rather than a potential 1,3-cyclization by indole N-alkylation suggested further uncertainty for completion of a catharanthine (**1**) synthesis.
5. A new disubstituted aldehyde **6** (Scheme 4) had to be synthesized to explore this convergent synthesis.

A = benzyl
or chiral directing substituents

seco-Ψ–vincadifformine products

cleavamine-type

R = H (**2**, coronaridine),
or alkoxy, alkylamino

Scheme 2.

Scheme 1, with subsequent formation of an isoquinuclidine from a 1,4-substituted aminocyclohexene, seemed operationally preferable to the dehydrosecodine sequence of Scheme 1.

We had found in 1995 that heating of the indoloazepine **3** with an excess of crotonal in toluene gave a 90% yield of the tetracyclic ester **4** by transient formation of the indoloacrylate dienamine **5**, and its intramolecular cyclization (Scheme 3).[7] The relative

Scheme 3. Reaction conditions: toluene, reflux 48 h, 90% yield.

Scheme 4. Reaction conditions: (a) LDA, HCO$_2$Me, THF, −78 °C; (b) ethylene glycol, TsOH, benzene, reflux, overall 76–90%; (c) LAH, THF, 0 °C, 100%; (d) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78 °C; (e) MeO$_2$CCH=P(C$_6$H$_5$)$_3$, 98% overall; (f) HClO$_4$, H$_2$O, CH$_2$Cl$_2$, 77–91%.

The synthesis of the aldehyde **6** (Scheme 4) begins with the formylation of methyl butanoate with methyl formate and lithium diethylamide to give the aldehyde ester **7**,[9] that could be derivatized to the acetal ester **8** with ethylene glycol and *p*-toluenesulfonic acid in 76% overall yield. Reduction of the ester with lithium aluminum hydride afforded the alcohol **9** (100% yield). Subsequent Swern oxidation of the alcohol **9** provided the aldehyde acetal **10**. A Wittig reaction of the aldehyde **10** with methyl

Scheme 5. Reaction conditions: 2 equiv **3**, toluene, cat. benzoic acid, 48 h refl., 14% **12**, 21% **13**.

(triphenylphosphoranylidene) acetate then furnished the acetal ester **11** (98% yield, two steps). Hydrolysis of the acetal function with perchloric acid gave the required crotonal **6** with ethyl and ester substituents in 91% yield (Scheme 4).

Heating of the indoloazepine **3** with the crotonal **6** and a catalytic amount of benzoic acid in toluene at reflux for 48 h, with addition of half of the indoloazepine **3** after 24 h, gave the isomeric condensation products **12** (14%) and **13** (21%), after separation by chromatography (Scheme 5). Trace amounts of epimeric esters, if present, were not isolated.

The stereochemistry of the desired tetracycle **12** was established by an X-ray crystal analysis (Figs. 1 and 2).

Comparison of the 2D ^{1}H NMR spectrum of product **12** with that of the isomer **13** showed the epimeric stereochemistry of the amine function in these compounds. A small coupling constant of δ_H 0.5 Hz between the olefinic methine hydrogen at δ_H 6.01 and the methine hydrogen adjacent to the ester function at δ_H 3.22 (near 90° angle, see Fig. 3, with ^{1}H and ^{13}C NMR assignments, shown as ent-**13** for increased clarity) ruled out near coplanarity of these hydrogens that would be expected for the secondary ester epimers

Figure 2. ent-**12** from X-ray.

of **12** and **13**. A detailed NMR analysis is given for compound **13** in Supplementary data.

With establishment that the tetracycle **12** has the requisite stereochemistry, efforts were undertaken to complete the total synthesis of catharanthine (**1**). Selective reduction of the less hindered ester function of product **12** by sodium borohydride in THF/methanol for 15–72 h gave the alcohol ester **14** (78–97% yields). Formation of a tosylate **15** (85%) and its debenzylation by hydrogenolysis in acetic acid then furnished the olefinic secondary amine **16** (69%). On heating the amino-tosylate **16** with diisopropylethylamine in THF, catharanthine (**1**) was formed in 76% yield, after chromatography and crystallization (Scheme 6).

An alternative second route to catharanthine (**1**) was also investigated through the intermediacy of the lactam **18** (Scheme 6). Debenzylation of the key aminodiester **12** by its hydrogenolysis in acetic acid provided the secondary amine **17** (100%). Heating of this diester in dioxane at 137 °C for 20 h in a sealed tube gave a mixture of starting material, some product with the desired molecular

Figure 1. X-ray structure of **12**.

Figure 3. *ent*-**13** with ^{1}H NMR and with ^{13}C NMR assignments.

Scheme 6. Reaction conditions: (a) NaBH$_4$, THF/MeOH, 15–72 h, 78–97%; (b) TsCl, cat. DMAP, THF, 3 h, 85%; (c) Pd/C, H$_2$, HOAc, 69%; (d) THF, *i*-Pr$_2$NEt, 3 h refl., 76%; (e) Pd/C, H$_2$, HOAc, 90%; (f) dioxane, 137 °C, 20 h; (g)[10] potential POCl$_3$, NaBH$_4$.

weight of oxocatharanthine **18** (identified by LC/MS, loss of one MeO, retention of indolic NH in NMR spectrum), and decomposition. When the lactam formation of **18** was attempted by heating at 125 °C for 48 h only the starting material **17** was recovered, while the attempted lactam formation at 150 °C for 20 h led mostly to decomposition, analogous to the thermal decomposition of catharanthine (**1**). If oxocatharanthine **18** had been produced in substantial yield, its reduction with phosphorousoxychloride and sodium borohydride could also have furnished catharanthine (**1**).[10] Heating the aminoester **17** at reflux in toluene with *p*-toluenesulfonic acid resulted in acylation of the indole nitrogen (loss of indolic NH, loss of one MeO group in NMR spectrum).

3. Conclusion

The principle of using an acyclic dienamine–indoloacrylate addition and a subsequent cyclization of the tetracyclic product **12** to an isoquinuclidine was established, resulting in a synthesis of catharanthine (**1**). The overall yield of catharanthine in this convergent new 11-step synthesis from methyl butanoate and an indoloazepine is 9% lower than the yield of our earlier convergent nine-step synthesis of catharanthine through a biogenetic dehydrosecodine mimic (Scheme 1),[1] primarily because of an unfavored diastereoselectivity in the key condensation step (formation of **12** vs **13**). A gratifying final isoquinuclidine ring-closure, rather than indole N-alkylation, completed the synthesis.

4. Experimental section

4.1. Methyl 2-formylbutyrate (7)[9]

Methyl butyrate (22.3 mL, 196 mmol) was slowly added to a cooled solution of LDA (293 mL of 2 M solution) in 400 mL of dry THF. The solution was stirred for 1 h at −78 °C, then methyl formate (60.3 mL, 979 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature for 1.5 h. The reaction mixture was then quenched with 1.5 L of water and extracted with pentane (3×200 mL). The aqueous layer was acidified with concd HCl to a pH of 2 and then extracted with diethyl ether (3×300 mL). The ether layer was washed with brine and dried over Na$_2$SO$_4$. Concentration yielded 23 g (177 mmol, 90%) of the condensation product **7**, which was used without further purification in the next step. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.71 (1H, d, *J*=2.4 Hz), 3.77 (3H, s), 3.19 (1H, m), 1.94 (2H, m), 1.00 (3H, t).

4.2. Methyl 2-(1,3-dioxolan-2-yl)butanoate (8)

A solution of the aldehyde **7** (25.9 g, 199 mmol), *p*-TsOH (0.76 g, 4 mmol), and ethylene glycol (13.3 mL, 239 mmol) in 450 mL of benzene was heated at reflux for 10 h with a Dean–Stark water trap. The solution was cooled to room temperature and quenched with 0.33 g (4 mmol) of NaHCO$_3$ in 300 mL of water. The two layers were separated and the aqueous layer was extracted with diethyl ether (3×200 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. Concentration yielded 31 g (178 mmol, 89%)

of the protected aldehyde **8**. Chromatography on silica gel, eluting with 10:1 hexane–ethyl acetate, and distillation at 120 °C/20 mm, gave a 76% overall yield for two steps. IR (film) ν_{max} 2969, 2880, 1740, 1435, 1273, 1200, 1155, 1099, 1029, 945 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.03 (1H, d, J=6.6 Hz), 3.98–3.93 (2H, m), 3.88–3.85 (2H, m), 3.72 (3H, s), 2.52–2.47 (1H, m), 1.75–1.69 (2H, m), 0.92 (3H, t, J=7.5); ^{13}C NMR (125 MHz, CDCl$_3$) δ 172.3, 103.7, 64.5, 51.7, 51.0, 20.6, 11.1; MS (CI) m/z (relative intensity) 175 ([M+H], 100%). Anal. Calcd for C$_8$H$_{14}$O$_4$: C, 55.16; H, 8.10. Found: C, 54.98; H, 8.25.

4.3. 2-(1,3-Dioxolan-2-yl)butan-1-ol (9)

LAH (5.2 g, 136 mmol) was added to 200 mL of anhydrous THF at 0 °C. Then methyl 2-(1,3-dioxolan-2-yl)butanoate (**8**, 13.58 g, 78 mmol) in 50 mL of anhydrous THF was added dropwise over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 6 h, then quenched with water and 10 g of NaOH was added. Extraction with ethyl acetate, several times, drying over sodium sulfate, concentration, and column chromatography (silica gel eluted with 5:1 hexane–ethyl acetate) afforded the pure alcohol **9** (11.34 g, 78 mmol, 100%) as a colorless oil. IR (film) ν_{max} 3445, 2964, 2880, 1466, 1401, 1158, 1107, 1041, 948 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.82 (d, J=4.3 Hz, 1H), 3.99–3.94 (m, 2H), 3.85–3.82 (m, 2H), 3.67–3.64 (m, 2H), 2.70 (br s, 1H), 1.74–1.69 (m 1H), 1.51–1.43 (m, 1H), 1.39–1.30 (m, 1H), 0.94 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 106.9, 64.9, 64.7, 61.6, 45.2, 19.5, 11.7. Anal. Calcd for C$_7$H$_{14}$O$_3$: C, 57.50; H, 9.66. Found: C, 57.40; H, 9.63.

4.4. 2-(1,3-Dioxolan-2-yl)butanal (10)

To 165 mL of anhydrous dichloromethane, cooled to −78 °C, were added dropwise oxalyl chloride (3.85 mL, 44.8 mmol) and anhydrous dimethyl sulfoxide (5.00 mL, 70.4 mmol). The reaction mixture was stirred at −78 °C for 5 min. Then the alcohol **9** (5.00 g, 34.2 mmol) in 50 mL of anhydrous methylene chloride was added dropwise over 30 min. The reaction mixture was stirred at −78 °C for another 30 min. Then anhydrous triethylamine (13 mL, 92.5 mmol) was added dropwise, and the reaction mixture stirred at −78 °C for 2.5 h, when TLC (3:1 hexane–ethyl acetate) showed completion of the reaction. The reaction mixture was concentrated and 100 mL of hexane was added to dissolve the product. The organic solution was passed through a silica gel plug funnel and concentrated to produce **10** as a light-yellow oil, which was used directly for the next step without further purification. ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.72 (d, 1H), 5.05 (d, 1H), 3.97 (m, 2H), 3.87 (m, 2H), 2.50 (m, 1H), 1.80 (m, 1H), 1.68 (m, 1H), 0.97 (t, 3H).

4.5. Methyl 4-(1,3-dioxolan-2-yl)hex-2-enoate (11)

The aldehyde **10** was dissolved in 80 mL of dry toluene, methyl (triphenylphosphoranylidene) acetate (12.6 g, 37.7 mmol) was added and the mixture heated at reflux for 12 h. Column chromatography (silica gel, 5:1 hexane–ethyl acetate) afforded the ester **11** (6.69 g, 33.4 mmol, 98% for two steps) as a colorless oil. IR (film) ν_{max} 2964, 2880, 1729, 1659, 1438, 1340, 1273, 1234, 1152, 1032 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.82 (dd, J=15.8, 9.2 Hz, 1H), 5.88 (d, J=15.8 Hz, 1H), 4.83 (d, J=4.2 Hz, 1H), 3.94–3.88 (m, 2H), 3.86–3.79 (m, 2H), 3.71 (s, 3H), 2.36 (tt, J=9.0 and 4.3 Hz, 1H), 1.73–1.66 (m, 1H), 1.47–1.40 (m, 1H), 0.89 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 166.7, 147.2, 123.4, 105.3, 65.2, 65.1, 51.5, 48.4, 22.2, 11.6; CIMS m/z (relative intensity) 201 ([M+H], 100%). Anal. Calcd for C$_{16}$H$_{16}$O$_4$: C, 59.97; H, 8.06. Found: C, 60.02; H, 8.10.

4.6. Methyl 4-formylhex-2-hexenoate (6)

The ester **11** (1.60 g, 7.99 mmol) was dissolved in dichloromethane (80 mL), perchloric acid (70%, 6 mL, 64.1 mmol) in water (10 mL) was added, and the reaction mixture stirred at room temperature for 48 h. Then it was diluted with water and extracted with dichloromethane. The extract was dried through sodium sulfate, concentrated and passed through a silica gel plug, eluting with 5:1 hexane–ethyl acetate, to afford the aldehyde **6** (1.14 g, 7.30 mmol, 91%). IR (film) ν_{max} 2972, 1743, 1689, 1438, 1203, 1174 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.40 (s,1H), 6.60 (t, J=7.0 Hz, 1H), 3.72 (s, 3H), 3.38 (d, J=7.1 Hz, 2H), 2.23 (q, J=7.6 Hz, 2H), 0.94 (t, J=7.7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 194.2, 170.3, 147.0, 143.7, 52.3, 33.7, 17.5, 12.9; MS (CI) m/z (relative intensity) 157 ([M+H], 100%).

4.7. cis- and trans-5-Benzyl-4-ethyl-2,4a,5,6,7,12-hexahydro-1H-benzo[2,3]azepino[4,5-b]indole-2,12b-dicarboxylic acid dimethyl ester (12 and 13)

A solution of methyl 4-formylhex-3-enoate (**6**, 0.46 g, 2.9 mmol), N-benzyl indoloazepine (**3**,[11] 0.47 g, 1.4 mmol), and a catalytic amount of benzoic acid in 25 mL of toluene was heated at reflux under nitrogen for 24 h. The reaction was monitored by TLC. Once the benzyl indoloazepine had been consumed, another portion of benzyl indoloazepine (**3**, 0.48 g, 1.4 mmol) was added with a catalytic amount of benzoic acid. Heating at reflux was continued for another 24 h when TLC showed completion of the reaction. Column chromatography on silica gel, eluting with 1:2.5 ethyl acetate–hexane gave first the cis-tetracycle **12** (0.19 g, 0.4 mmol, 14%), followed by the trans-tetracycle **13** and trace amount of product with R_f 0.33, 2.5:1 hexane–ethyl acetate.

For product **12**: Recrystallized from CH$_2$Cl$_2$, mp 205–206 °C; TLC R_f 0.44, 2.5:1 hexane–ethyl acetate, gray-yellow ceric ammonium sulfate stain; IR (film) ν_{max} 3389, 2947, 1737, 1460, 1432, 1245, 1194, 1163, 1136, 738 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.07 (s, 1H), 7.47–7.08 (m, 9H), 5.73 (s, 1H), 4.61 (s, 1H), 4.06 (d, J=13.7 Hz, 1H), 3.96 (d, J=13.7 Hz, 1H), 3.70 (s, 3H), 3.64 (s, 3H), 3.54–3.49 (m, 1H), 3.34–3.29 (m, 1H), 3.24–3.13 (m, 2H), 2.91–2.86 (m, 1H), 2.78 (dd, J=14.0, 7.2 Hz, 1H), 2.48 (dd, J=14.0, 11.0 Hz, 1H), 2.36 (q, J=7.5 Hz, 2H), 1.23 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.9, 173.7, 141.8, 140.4, 135.3, 132.7, 128.8, 128.2, 128.1, 126.6, 122.3, 121.1, 119.2, 118.5, 112.2, 110.4, 62.2, 55.4, 52.7, 52.0, 51.6, 50.9, 40.7, 31.7, 28.6, 22.4, 12.4 ppm; EIMS m/z (rel intensity) 472 (22, M$^+$), 261 (18), 259 (19), 258 (100); HRMS Calcd for C$_{29}$H$_{32}$N$_2$O$_4$: 472.23621. Found: 472.23726. Anal. Calcd for C$_{29}$H$_{32}$N$_2$O$_4$: C, 73.71; H, 6.83; N, 5.93. Found: C, 73.56; H, 6.94; N, 5.89.

For product **13**: TLC R_f 0.29, 2.5:1 hexane–ethyl acetate, gray-yellow ceric ammonium sulfate stain; IR (film) ν_{max} 3395, 2952, 1726, 1460, 1435, 1225, 912, 733; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.25 (s, 1H), 7.50–7.08 (m, 9H), 5.98 (s, 1H), 4.47 (s, 1H), 4.16 (d, J=15.3 Hz, 1H), 3.77 (s, 3H), 3.58 (d, J=18.5 Hz, 1H), 3.56 (s, 3H), 3.25–3.12 (m, 4H), 3.07 (t, J=7.8 Hz, 1H), 2.81 (dd, J=15.8, 7.5 Hz, 1H), 2.48 (dq, J=14.9 and 7.6 Hz, 1H), 2.26 (dd, J=13.7 and 7.6 Hz, 1H), 2.18 (dq, J=14.6 and 7.3 Hz, 1H), 1.15 (t, J=7.3 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 173.7, 173.5, 141.9, 139.8, 136.9, 134.9, 128.3, 128.1, 127.5, 126.5, 121.9, 120.1, 119.3, 118.3, 114.3, 110.7, 65.8, 52.7, 52.1, 51.9, 48.6, 39.0, 33.2, 28.5, 21.5, 13.6; EIMS m/z (rel intensity) 472 (29, M$^+$), 261 (28), 259 (22), 258 (100); HRMS Calcd for C$_{29}$H$_{32}$N$_2$O$_4$: 472.2362. Found: 472.2360.

4.8. cis-5-Benzyl-4-ethyl-2-hydroxymethyl-2,4a,5,6,7,12-hexahydro-1H-benzo[2,3]azepino[4,5-b]indole-12b-carboxylic acid methyl ester (14)

To a solution of the tetracyclic diester **12** (370 mg, 0.783 mmol) in 50 mL of 1:1 THF–methanol a large amount of sodium

borohydride was added and the mixture was heated at reflux for 3 days. Addition of 30 mL of water, extraction with methylene chloride and column chromatography on silica gel (5:1 hexane–ethyl acetate) gave the alcohol **14** (273 mg, 0.614 mmol, 78%) as a colorless solid. A reduction of 42 mg of **12** at room temperature gave a 97% yield. Crystallized from CH_2Cl_2–hexane, mp 140–141 °C; TLC R_f 0.11 (EtOAc–hexanes, 1:2.5); IR (film) ν_{max} 3389, 2958, 2930, 2874, 1717, 1494, 1460, 1239, 1164, 1136, 1043, 738 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.18 (s, 1H), 7.46–7.06 (m, 9H), 5.62 (s, 1H), 4.63 (s, 1H), 4.03 (d, J=13.8 Hz, 1H), 3.94 (d, J=13.8 Hz, 1H), 3.68 (s, 3H), 3.57 (d, J=4.2 Hz, 1H), 3.32–3.26 (m, 1H), 3.20–3.12 (m, 2H), 2.95–2.85 (m, 1H), 2.70–2.55 (m, 2H), 2.33 (q, J=7.5 Hz, 2H), 1.99 (dd, J=12.7, 9.9 Hz, 1H), 1.12 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.2, 141.5, 140.6, 135.3, 133.4, 128.8, 128.2, 128.1, 126.6, 124.5, 122.1, 119.1, 118.5, 111.8, 110.3, 66.8, 62.4, 55.7, 52.5, 51.8, 51.3, 37.3, 33.0, 28.7, 22.5, 12.5; CIMS m/z (rel intensity) 445 (15, M$^+$), 431 (100); CI HRMS Calcd for $C_{28}H_{33}N_2O_3$: 445.2491. Found: 445.2486.

4.9. *cis*-5-Benzyl-4-ethyl-2-(toluene-4-sulfonyloxymethyl)-2,4a,5,6,7,12-hexahydro-1*H*-benzo[2,3]azepino[4,5-*b*]indole-12b-carboxylic acid methyl ester (15)

To a solution of the tetracyclic alcohol **14** (220 mg, 0.495 mmol) in 20 mL of anhydrous THF were added tosyl chloride (142 mg, 0.742 mmol) and a catalytic amount of DMAP. The mixture was stirred at room temperature for 3 h, then concentrated and column chromatographed (silica gel, 1:2.5 ethyl acetate–hexane) to give a colorless solid (251 mg, 0.419 mmol, 85%); mp 169–170 °C; TLC R_f 0.34 (EtOAc–hexanes, 1:2.5); IR (film) ν_{max} 3406, 2961, 1722, 1460, 1359, 1242, 1188, 1176, 964, 910, 815, 739, 666 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (s, 1H), 7.63 (d, J=8.2 Hz, 2H), 7.44 (d, J=7.9 Hz, 1H), 7.28–7.25 (t, 3H), 7.22 (d, J=6.9 Hz, 1H), 7.16–7.14 (t, 5H), 7.07 (t, J=7.8 Hz, 1H), 5.41 (s, 1H), 4.57 (s, 1H), 3.98–3.91 (m, 2H), 3.81 (dd, J=13.7 Hz, 2H), 3.66 (s, 3H), 3.27–3.24 (m, 1H), 3.16–3.08 (m, 2H), 2.87–2.82 (m, 2H), 2.55 (dd, J=6.6 Hz, 1H), 2.32 (s, 3H), 2.29–2.19 (m, 2H), 1.84 (dd, J=10.9 Hz, 1H), 1.06 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 174.5, 145.4, 143.4, 140.9, 136.0, 133.5, 130.4, 129.4, 128.9, 128.8, 128.5, 127.4, 123.2, 123.0, 120.0, 119.2, 112.7, 111.1, 73.6, 63.1, 61.1, 56.2, 53.4, 52.3, 51.6, 35.0, 33.4, 29.2, 23.1, 22.3, 21.8, 14.9, 13.1; HRMS neg. ion mode, 1:1 CH$_3$CN–H$_2$O, Calcd for $C_{35}H_{38}N_2O_5S$: 598.250. Found: 598.246.

4.10. *cis*-4-Ethyl-2-(toluene-4-sulfonyloxymethyl)-2,4a,5,6,7,12-hexahydro-1*H*-benzo[2,3]azepino[4,5-*b*]indole-12b-carboxylic acid methyl ester (16)

A solution of the tetracylic tosylate **15** (16 mg, 0.0267 mmol) and 10 mg of 10% Pd/C in 2 mL of acetic acid was stirred for 5 h under hydrogen. The acetic acid was removed under low pressure and the residue was neutralized with triethylamine. Column chromatography (silica gel, 1:2.5 ethyl acetate–hexane) gave a light-yellow solid as the product (9.4 mg, 0.0185 mmol, 69%). The product was used directly for the next step. TLC R_f 0.71 (EtOAc).

4.11. (±)-Catharanthine (1)

A solution of the tetracylic alcohol tosylate **16** (9.4 mg, 0.0185 mmol) and DIPEA (0.10 mL, 0.0574 mmol) in 20 mL of dry THF was heated at reflux under nitrogen for 3 h. The reaction mixture was concentrated and column chromatographed (silica gel, 1:2.5 ethyl acetate–hexane) to give a light-yellow solid (5 mg, 0.0149 mmol, 76%). Its mp 173 °C matched racemic catharanthine (**1**)[1,2] and its ^{1}H NMR and ^{13}C NMR spectra matched those of natural catharanthine (**1**).

4.12. *cis*-4-Ethyl-2,4a,5,6,7,12-hexahydro-1*H*-benzo[2,3]azepino[4,5-*b*]indole-2,12b-dicarboxylic acid dimethyl ester (17)

A solution of 36 mg (0.76 mmol) of the *N*-benzyl diester **12** in 5 mL of acetic acid was stirred with 10 mg of 10% Pd/C under a hydrogen atmosphere for 20 h. The mixture was poured onto ice, basified with dilute sodium hydroxide, and extracted with dichloromethane to give 29 mg (100%) of debenzylation product **17**, which crystallized from hexane with mp 150–151 °C; TLC R_f 0.33 (2.5:1 hexane–ethyl acetate); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.00 (s, 1H), 7.49 (d, J=5.0, 1H), 7.26 (d, J=5.0, 1H), 7.16 (t, J=7.0, 1H), 7.08 (t, J=7.0, 1H), 5.47 (br s, 1H), 4.01 (s, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.45–3.39 (m, 2H), 3.21–3.09 (m, 2H), 2.95–2.89 (m, 1H), 2.59–2.55 (m, 1H), 2.50–2.43 (m, 1H), 2.30–2.16 (m, 2H), 1.80 (s, 1H), 1.08 (app. t, J=7.4, 3H); EIMS m/z (rel intensity) 382 (90, M$^+$), 351 (7), 323 (14), 215 (80), 168 (100), 154 (18); HRMS Calcd for $C_{22}H_{26}N_2O_4$ 382.1893. Found: 382.1896. Heating of this product at 125 °C in 5 mL of dry dioxane, in a sealed tube, for 48 h, gave complete recovery with matching TLC and ^{1}H NMR spectrum.

5. Crystallographic data

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC# 682781. Unit cell parameters: *a* 15.934 (2), *b* 15.043 (4), *c* 10.542 (2), β 92.17 (1), space group *P*21/*c*. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc. cam.ac.uk).

Supplementary data

^{1}H and ^{13}C NMR and IR spectra for compounds **1**, **6**, **9**, **11**, **12**, **13**, **14**, **15**, and ^{1}H NMR spectra for compounds **16** and **17**. Mass spectra for compounds **12**, **13**, **14**, **17**. X-ray crystallographic data for compound **12**. 2D NMR analysis[12–16] with NOE and HMBC diagram for compound **13**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.044.

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